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Water-soluble polyol-methanofullerenes as mitochondria-targeted antioxidants: Mechanism of action

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ABSTRACT

The mechanism of an antioxidant action of water-soluble polyol – methanofullerenes $C_{60}[C_9H_{10}O_4(OH)_4]_6$ and $C_{60}[C_{13}H_{18}O_4(OH)_4]_6$ as the mild uncouplers of an oxidative phosphorylation and respiration is postulated. According to this mechanism, hydroxyl group of methanofullerenols can be protonated under excess of protons in the intermembrane space of hyperpolarized mitochondria. Protonation of fullerene derivatives is confirmed by the decrease in their negative Zeta potential in the pH below 5.4. Heavily protonated methanofullerenols become positively charged and move into the mitochondrial matrix. As a consequence, the proton gradient is dissipated, which causes a decrease in mitochondrial transmembrane potential ($\Delta\Psi_m$) and reduction in ROS production.

Increased production of the reactive forms of oxygen (ROS) by mitochondria (oxidative stress) is linked to some dangerous pathological conditions (neurodegenerative diseases, cancer, aging, etc.). The oxidative stress depends on the magnitude of the mitochondrial transmembrane potential ($\Delta\Psi_m$): the higher $\Delta\Psi_m$ the more of the free radicals the mitochondria produce.[1] The damage associated with the increased production of ROS can be mitigated by the uncouplers of respiration and phosphorylation. The protonophores transport protons through the inner mitochondrial membrane that leads to a drop in the $\Delta\Psi_m$ and uncoupling of the respiration and phosphorylation. The mild uncouplers of oxidative phosphorylation – lipophilic cations capable to reversibly bind protons were patented by Skulachev et al.[2] Their ability to uncouple depends on the magnitude of the $\Delta\Psi_m$ in mitochondria. The mild uncouplers, which are able to do both: to dissipate the high $\Delta\Psi_m$ and to deactivate the already existing oxygen radicals, are of particular value.[3] In this regard, water-soluble methanofullerenols $C_{60}[C_9H_{10}O_4(OH)_4]_6$ and $C_{60}[C_{13}H_{18}O_4(OH)_4]_6$, which exhibit the properties of mitochondrial uncouplers[4] and preserve the antioxidant capacity of fullerene C_{60},[5] look very promising. In addition, both methanofullerenols are soluble at the physiological range of pH (4–8),[6] nontoxic[7,4] and retain lipophilic properties of the fullerene C_{60}, which is essential for the movement across cellular membranes. In this communication, we propose and validate a mechanism of uncoupling action of these fullerene derivatives.

Previously, the possible mechanism of an antioxidant action of C_{60} fullerene has been proposed on the basis of computer simulation by the method of the density functional theory (DFT). According to this mechanism, the protons can penetrate fullerene's surface and give the fulleren a positive charge, which allows C_{60} to cross the inner mitochondrial membrane. It is believed that these proton–confining fullerenes transfer the protons through the inner mitochondrial membrane to the mitochondrial matrix leading to a drop in the $\Delta\Psi_m$.[8] However, this mechanism of antioxidant action of unmodified fullerenes is still to be experimentally confirmed.

We had previously shown on the model of the yeast *Yarrowia lipolytica* (obligate aerobic eukaryotic cells) that water-soluble fullerene derivatives, $C_{60}[C_9H_{10}O_4(OH)_4]_6$ and $C_{60}[C_{13}H_{18}O_4(OH)_4]_6$, did reduce the $\Delta\Psi_m$, while preserving basic morphological parameters of cells (i.e. cell size and granularity), which allowed us to attribute these compounds to a potential mitochondria-targeted antioxidants.[4] In contrast to an unmodified fullerene, the methanofullerenols have the electronegative hydroxyl groups on their surface. We believe that these groups are responsible for protonophore properties of the investigated fullerene derivatives.

It is known that the fullerene surface has electron acceptor properties.[5] The oxygen of the hydroxyl groups in the structure of the tested methanofullerenols contains unshared pairs of

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